# Exhibit 17

# Inherent Method Variability in Dissolution Testing:

# The Effect of Hydrodynamics in the USP II Apparatus

A Technical Report Submitted to the Food and Drug Administration

by

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## *Introduction*

Dissolution testing is routinely carried out in the pharmaceutical industry to determine the rate of dissolution of solid dosage forms. In addition to being a regulatory requirement, in-vitro dissolution testing is used to assist with formulation design, process development, and the demonstration of batch-to-batch reproducibility in production. The most common of such dissolution test apparatuses is the USP Dissolution Test Apparatus II, consisting of an unbaffled vessel stirred by a paddle, whose dimensions, characteristics, and operating conditions are detailed by the USP (Cohen et al., 1990; The United States Pharmacopeia & The National Formulary, 2004).

Despite its widespread use in the industry, relatively little information was available until recently on the hydrodynamics of this dissolution apparatus and the effects of operating and geometric variables on the velocity distribution in the system. Such information is critical to advance the fundamental understanding of the dissolution rate process, enhance the reliability of dissolution testing, and eliminate artifacts associated with test methods, especially since dissolution measurements have often been reported to be inconsistent and poorly reproducible. In fact, failed dissolution tests resulted in 47 product recalls in 2000–2002, representing 16% of non-manufacturing recalls for oral solid dosage forms (FDC Reports, 2001, 2002, 2003). Failed dissolution test can result in product recalls, costly investigations, potential production delays, all of them having substantial financial impact to the pharmaceutical industry

A review of the literature shows that there have been numerous reports describing high variability of test results, even for dissolution apparatus calibrator tablets (Cox and Furman, 1982; Moore et al., 1995; Qureshi and Shabnam, 2001). Even more significantly, the hydrodynamics of the Apparatus II appears to play a major role in the poor reproducibility of dissolution testing data and the inconsistency of dissolution results. This is not surprising considering that the Apparatus II is a small, unbaffled vessel with a hemispherical bottom provided with a slowly rotating paddle, in which a tablet (or another dosage form) is dropped. As it has been know for decades to reaction engineers, such a system would be only be capable of incipient turbulence, which is characterized

by substantial spatial heterogeneity in energy dissipation rate, which would have a direct impact on mass transfer rates and, consequently, on dissolution.

The tablet dissolution process is intrinsically complex since it involves solid-liquid mass transfer, particle erosion, possible particle disintegration, particle suspension and particle-liquid interactions. However, this process is further complicated by the interaction of the complex tri-dimensional flow with the dissolving tablet and its fragmented particles, the highly variable velocity, energy, and shear stress distribution as a function of tablet location within the apparatus, and the uncertainty in the location of the tablet upon its release inside the apparatus. Literature reports confirm these observations and the potentially important role of hydrodynamics on the dissolution process and the inconsistency of dissolution test results (Mauger et al., 2003; Healy et al., 2002; Moore et al., 1995; Qureshi and McGilveray, 1999, Qureshi and Shabnam, 2001; Costa et al., 2001; Boccanegra et al., 1990; Cox et al., 1983, Cox and Furman, 1982).

Over the years, much of the intrinsic variability of the test has been in fact recognized and attempted to be addressed by using calibrator tablets to try to quantify it. The concept is simple: if highly uniform product gives variable results, this degree of variability can be attributed to the method and therefore subtracted from the variability observed in the product. Unfortunately, this attempt to resolve the complex issue of test variability is unlikely to succeed, for (three) reasons:

(1) There is no realistic way to assure *a priori* that the so-called calibrator tablets are indeed free of variability (if we knew how to remove variability from calibrator tablets, we would know how to remove variability from actual solid dosage products, hence making dissolution testing unnecessary);

(2) The degree of test-related variability for a given product is likely to depend on tablet weight, shape, and "stickiness", and thus be different than the variability experienced by calibrator tablets, thus rendering the approach void of value even if "perfect calibrator tablets" were indeed available.

(3) The mechanism of tablet disintegration and/or release may or may not be the same as for the calibrator and may, therefore, exhibit different response(s) to the variability in the dissolution test.

A much sounder approach is to use well established scientific principles to DESIGN a test that is free of hydrodynamic-induced variability. The methods to achieve this goal have been available for more than a decade, and are the same methods used in the next section to demonstrate the nature of the problem.

## *Effect of Hydrodynamics of Velocity Distribution, Shear Stress, and Dissolution Profiles for the Standard Dissolution Test Case*

The velocity and shear stress/strain distribution are basic tools of fluid mechanical phenomena affecting tablet disintegration, mixing, and mass transfer. The velocity vectors yields information on the direction and speed of the flow at any point while the strain rates highlight how the fluid interacts with the vessel and other objects (such as the tablet, paddle etc.) which ultimately impacts on the thickness of the static boundary layer on tablet and fragment surfaces and dissolution rates.

A significant amount of new results have been recently generated by our two research groups at NJIT (Armenante) and Rutgers University (Muzzio). In these investigations, the hydrodynamics of the dissolution apparatus was studied both computationally and experimentally in significant detail using independent methods. In addition, dissolution tests were conducted at Rutgers with tablets placed at specific locations in the system selected to correspond to the maximum and mininmum shear rates along the vessel bottom, respectively. All these results clearly show that the velocity and shear distributions as well as the dissolution test profiles are greatly affected by the location of the tablet and minor changes to the geometry of the system (Kukura et al., 2002; Kukura et al., 2003, Baxter et al., 2005; Bai et al., 2005; Armenante et al., 2004; Armenante et al., 2003). *The present document intends to examine such recent results in order to show how the hydrodynamics of the system can introduce a significant level of variability in the process and can significantly affect the results of dissolution testing.*

The NJIT group under Prof. Armenante (2005; Bai et al., 2005; Armenante et al., 2004; Armenante et al., 2003) studied the hydrodynamics of dissolution testing using Laser-Doppler Velocimetry (LDV) and Computational Fluid Dynamics (CFD), respectively, to experimentally map and computationally predict the velocity distribution and the turbulent intensity inside a standard USP Apparatus II under the typical operating conditions mandated by the dissolution test procedure (900 mL fill level; distance of 25 mm between the blade and the inside bottom of the vessel; 50 rpm, corresponding to Re=4688). These researchers measured the three velocity components, including the fluctuating components, at 7 different radial locations on 10 horizontal planes (Figure 1). An example of the data that they collected is presented in Figure 2, which also shows the predictions from their CFD simulations for the tangential velocities on three horizontal planes. Substantial agreement between the CFD prediction and the LDV data was obtained, thus validating the CFD approach. These investigators produced plots of the velocity distribution profiles (tangential, axial, and radial), contours of velocity magnitude (on vertical and horizontal cross sections); velocity vectors (on vertical and horizontal cross sections), contour plots of strain rates on vertical cross sections, and contour plots of the specific energy dissipation rates on vertical cross sections. Figure 3 shows show an example of the contours of the velocity magnitude on two vertical cross sections through the shaft at two perpendicular orientations of the paddle. Similar plots showing velocity vectors on vertical cross sections are presented in Figure 4. The greater vector density in some locations of the vessel is an artifact reflecting the greater concentration of cells in those regions, as also shown in the pictures of the simulation mesh. The flow in the region below the paddle is shown in greater detail in Figure 5. These figures show that the flow is relatively strong in the tangential direction, even in this region below the paddle, but weak in the radial and axial components leading to "dead spaces". Below the paddle one can detect the presence of a second vertical recirculation loop having a stronger pulsating component generated by the passing of the blade. When this pulsating effect decays the flow is extremely weak. However, the striking feature of the flow in this region is that this vertical recirculation loop is not able to penetrate the inner core region located under the paddle. **The net result is that the flow under the paddle shaft is nearly stagnant in the vertical plane** and it is composed only of weak tangential velocities of the order of 5% of the tip speed or less. **This weakly swirling but otherwise nearly stagnant core region extends all the way from the vessel bottom to the lower edge of the paddle.** At its vertical boundaries, the axial velocities change rapidly with time and location, while still remaining very weak. This analysis can qualitatively explain the effect of "coning" at the center of the vessel bottom. Coning is often observed when a tablet disintegrates rapidly during the dissolution test, and the resulting granules form a rotating cone of loosely aggregating particles under the paddle. These figures show that the velocity flow field near the tank bottom, i.e., where the tablet lies, changes rapidly with position, implying that **the exact location where the tablet lands after it is dropped in the vessel may have a dramatic effect on the velocity field surrounding the tablet**.

Experiments conducted by Hamlin et al. (Hamlin et al., 1962) have shown that variation in the boundary layer thickness due to changing agitation speeds can compromise the ability of the in vitro dissolution test to predict in vivo performance. The thickness of the boundary layer at the surface of the tablet is controlled by the shear forces exerted by the fluid. Figure 6 and, in greater detail, Figure 7 present the shear rate (directly proportional to the shear stress) in the vessel. It is obvious from this figures that the shear rate varies very significantly with position along the vessel bottom, implying that if two tablets land at different locations they may experience very different hydrodynamic flow fields, and consequently different mass transfer and dissolution rates.

The NJIT group also conducted CFD simulations in which a tablet placed just under the paddle was introduced. The results for the overall velocity distribution, the velocity distribution near the vessel bottom, and the shear strain rate, also near the bottom, for this case are reported in Figures 8, 9, and 10, respectively. One can clearly see that the top face of the tablet is in a nearly stagnant region, and experiences very little shear rate. If the tablet is at a different locations on the vessel bottom — for example away from the centerline — it would be surrounded by a completely different flow field and experience a different shear rate that will affect its dissolution rate.

These conclusions are confirmed and reinforced by the results obtained concurrently by the Rutgers University research group under Prof. Muzzio (Kukura et al., 2002; Kukura et al., 2003, Baxter et al., 2005) using entirely different methods: Particle Imaging Velocimetry was used to characterize velocity fields experimentally, and Finite-Element simulations were used to quantify shear rates. Figure 11 shows the average strain rate along the vessel bottom. Significant differences exist depending on the location, especially if the strain rate under the shaft is chosen as the reference value. This figure supports the results of Figure 7. Figure 12 actually shows that the tablet moves slightly under the action of the rotating flow field shown in Figures 4 and 5.

Even more interesting however are the results of the dissolution data reported in Figure 13 by Muzzio and coworkers, who conducted dissolution test with three types of tablets i.e., prednisone calibrator tablets, (b) salicylic acid calibrator tablets, and (c) naproxen sodium tablets. In these experiments the tablet location was carefully controlled by preparing a circular ring on the inner dish of the dissolution vessel using silicone glue, 11 mm in diameter, in which the tablet could be placed. Two positions were tested; one in which the tablet was centered at the bottom of the vessel, the other in which the ring was positioned 21 mm from the center, selected to correspond to locations of minimum and maximum shear, respectively.

Comparing the overall experiments, more than a two-fold difference in the measured dissolution rate was observed between the experiments at the two prednisone tablet locations. (An added element of possible variability can also be seen from the studies in the velocity distribution above the paddle. It is clear that *where and how a* sample is taken may also impact on the value obtained. The data summarized here assumes that any artifact derived from the *position* at which the sample is taken is ignored.) Statistical analysis showed a difference factor of 146.2 and a similarity factor of 31.5, clearly indicating that the two profiles are not statistically similar by this technique. The dissolution profiles for the salicylic acid calibrator tablets show that the dissolution rate is observed to be higher for the tablets measured in the off-centered position. The dissolution–time curve for the naproxen sodium tablets shows that a 70% average difference is observed between the experiments performed in the centered position and those performed in the off-centered position. A difference factor of 73.2 and a similarity factor of 28.1 both confirm the positions to be statistically different. ANOVA also shows the two positions to be statistically different at all time points along the curve.

In conclusion, the results obtained by the above-mentioned research teams in terms of CFD simulations of the velocity profiles (validated through LDV and PIV) and dissolution tests show that significant differences exist in the flow rate and shear rate at different locations near the tank bottom of a USP Dissolution Apparatus II, and that these difference occurs rapidly over short distances. In particular, a nearly stagnant region exists below the shaft. Therefore, the exact location of the tablet is critical for the magnitude of the flow field and shear rate that it will experience, and hence its dissolution rate. Given the randomness of the settling process of the tablet after it is released in the vessel, this factor alone is likely to introduce significant uncertainty in the results of the test. The dissolution experiments reported here clearly show that the tablet location is a key variable.

## *Science-Based Approach to Dissolution Testing*

Over the years, several methods have been developed to deal indirectly with the hydrodynamic effects reported here. These include the use of the PEAK vessel to exclude the central region, the use of "sinkers" to ensure tablets go to the bottom of the vessel, the positioning of the paddle off-center, and others. While these attempts show recognition on the part of the pharmaceutical community of the problems associated with dissolution testing, they still fail to address the fundamental issues described above.

Our groups believe that none of these interesting modifications constitute a robust approach for modifying the essential fact that the transitional-Reynolds-number (the dimensionless number to signal the transition from laminar to turbulent flow, which has a transitional range during which flow is neither all laminar nor fully turbulent) flow in this test (and in similar other tests where the intensity of flow is of the same order of magnitude) is intrinsically variable with respect to position and time, and that this non-uniform environment is likely to introduce unexpected variability in test results. Future products will interact in unexpected ways with a non-uniform environment, and in our opinion, will continue to generate test-related failures.

Rather than continue to tinker with what is, in essence, a poorly designed starting point, we propose to the US FDA and to the distinguished committee to recommend and/or initiate the use of engineering principles and methods to design a test where the flow is spatially and temporally homogeneous and does not introduce undue variability. The design of such a system can be accomplished in a relatively short time and its performance can be rigorously tested using a strong toolbox of theoretical and experimental methods that have been used in many other modern enterprises to design airplanes that do not crash, build bridges that do not collapse, and petroleum refineries that achieve optimum product mix in spite of strong raw material variability.

## *Conclusions and Recommendations*

The velocities in the region below the paddle in the USP II Dissolution Apparatus II were found to be very low in magnitude. In particular, the lowest region just below the shaft is characterized by extremely low velocities. This is the most critical region of the apparatus since the dissolving tablet will likely be at this location during the dissolution test. The velocities in this region, although very small, change significantly over short distances along the vessel bottom. This shows that small variations in the location of the tablet on the vessel bottom caused by the randomness of the tablet descent through the liquid are likely to result in significantly different velocities and velocity gradients near the tablet. This is likely to introduce variability in the test, as it has been confirmed experimentally in controlled dissolution test where the tablet was placed at different fixed locations.

The slowly rotating, nearly quiescent zone below the shaft is likely to be responsible for the coning phenomenon that is often observed as the tablet disintegrates during dissolution, and the fragments accumulate below the paddle in the shape of a cone. The velocity profiles in this nearly quiescent zone and the size of this zone do not appear to change appreciably with increasing agitation speeds. However, the velocities surrounding this zone, as well as the velocity profiles in all other the regions of the vessel do change in approximately direct proportion to the paddle speed. Therefore, particles outside the nearly quiescent zone are likely to experience very different fluid dynamic conditions that can possibly result in their transfer out of the quiescent region, their suspension, and the elimination of coning with increasing paddle speed.

Perhaps the most important observation to be made at this point is that the problems identified here with the USP II apparatus, far from being an isolated phenomenon, are the proverbial "tip of the iceberg" of a generally weak understanding of the fundamental scientific principles underlying mechanical effects on unit dose dissolution testing. Our two teams, working independently, properly applying mature engineering techniques easily identified the problems mentioned above. Further, we agree that a "localized treatment" to these problems will simply delay addressing the fundamental issue: quality tests of critical importance need to be designed from first principles using the best available science. While it is always possible to ignore the underlying issues and delay the necessary effort to solve this problem in a robust manner, doing so will be costly and risky. A highly variable test leads to both Type I and Type II errors: release of defective product and failure of good product. The public and the industry deserve better.

Our joint recommendations to the FDA and to the distinguished advisory committee are as follows:

(1) Recognize that dissolution testing, in its present form, is based on a weak understanding of relevant mechanical principles
(2) Abandon the practice of pre-assigning variability to the test based on the use of calibrator tablets. In its current embodiment, product variability and test variability cannot be de-coupled
(3) Abandon the practice of calibrating dissolution equipment. The instrument is simple. If properly operated, there should be no need to calibrate it (of course it must be properly maintained)
(4) Adopt criteria based on total variability, until a better test devoid of intrinsic variability is designed, optimized, and implemented
(5) Launch a long term effort to understand unit dose drug release from first principles, and use the enhanced scientific understanding to design a better test,

***or even better,***

(6) Improve the understanding of the effect of ingredient properties and processing conditions on product quality, thus making the test unnecessary.

Our laboratories remain committed to assisting the FDA and industry to the full extent of our capabilities in achieving these recommendations.

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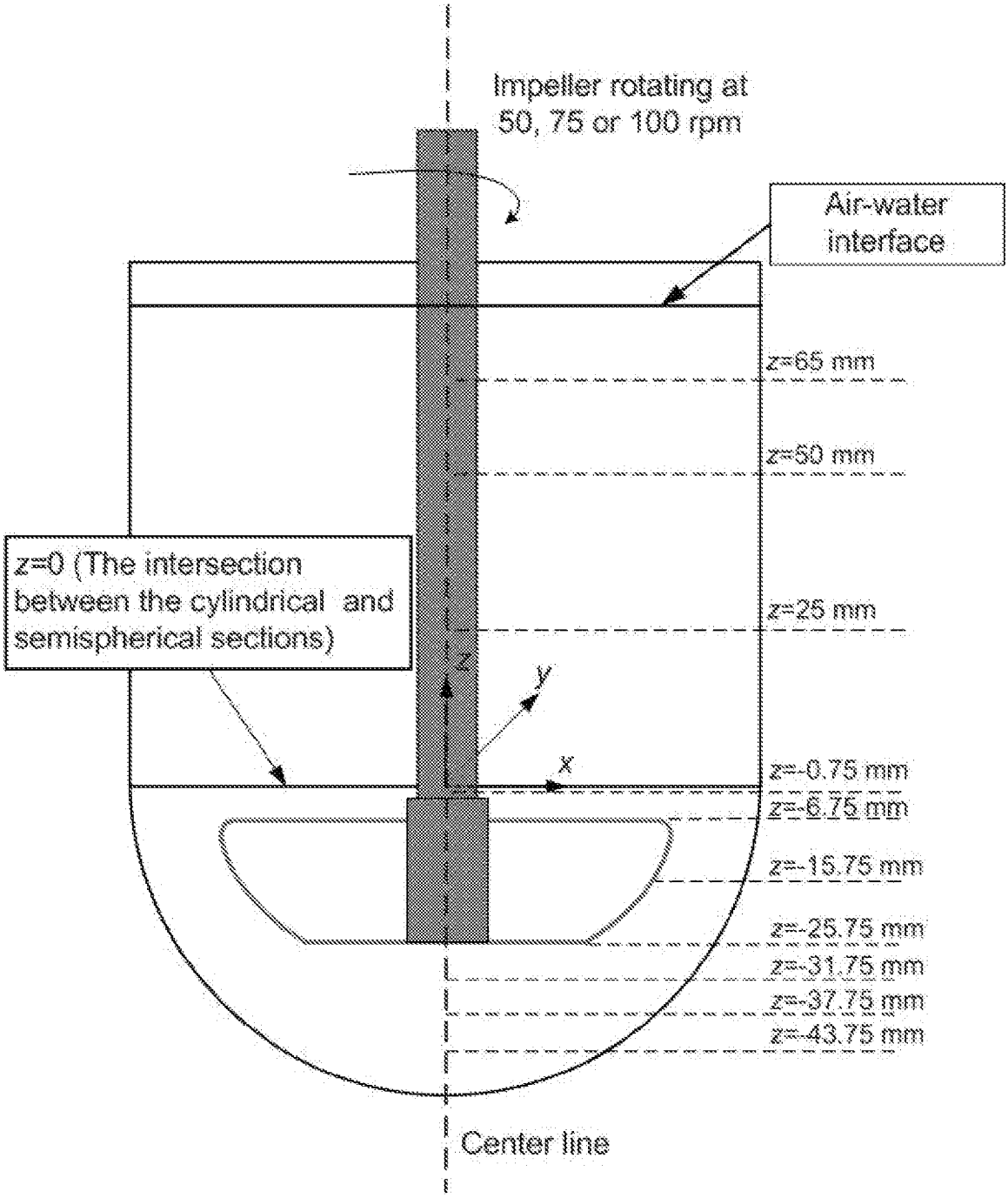



Figure 1. Location of iso-surfaces where local velocities were experimentally measured via LDV.

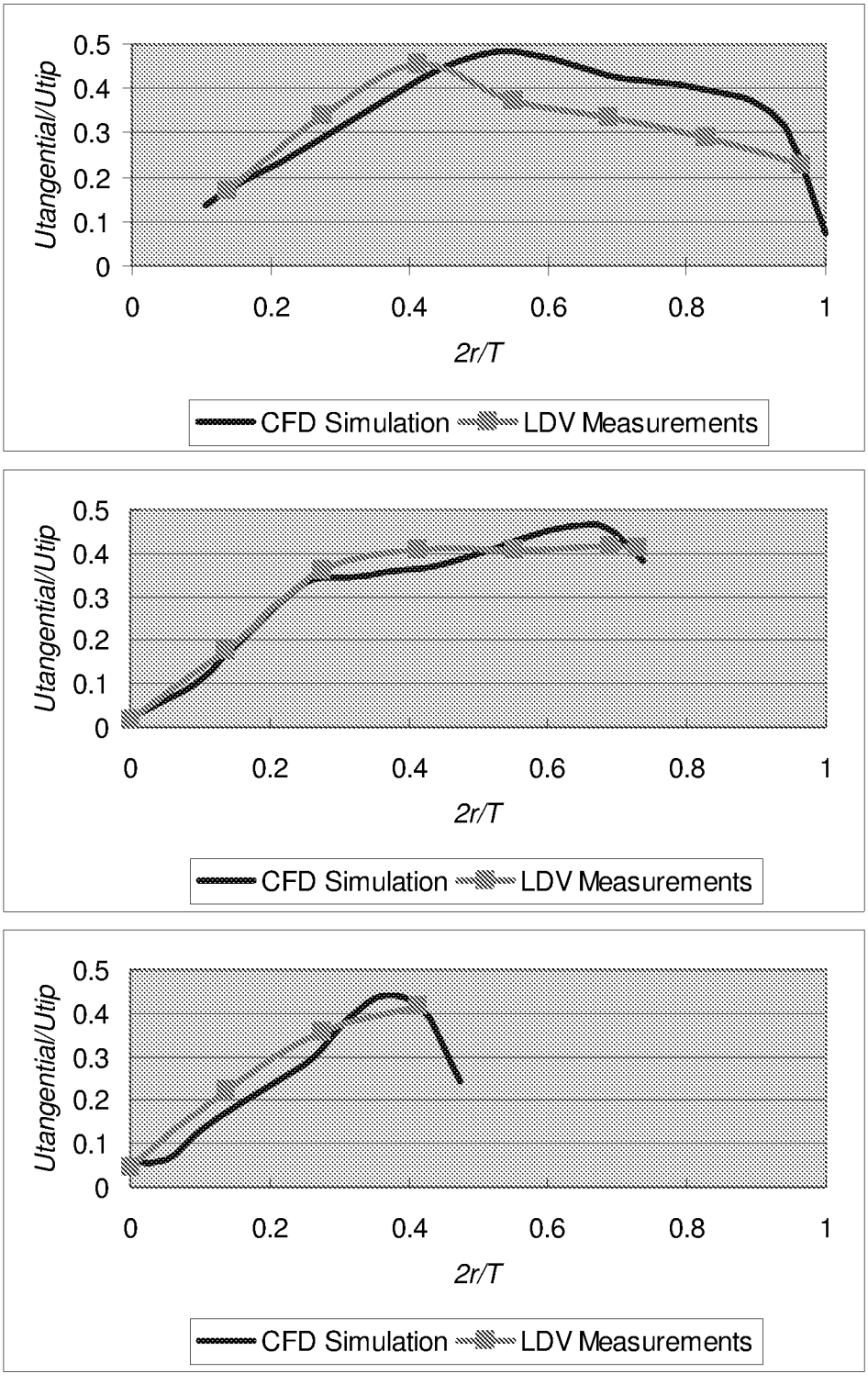



Figure 2. Tangential Velocities on different horizontal planes, at z=65mm (top panel), z=-31.75mm (middle panel), and z=-43.75mm (bottom panel)

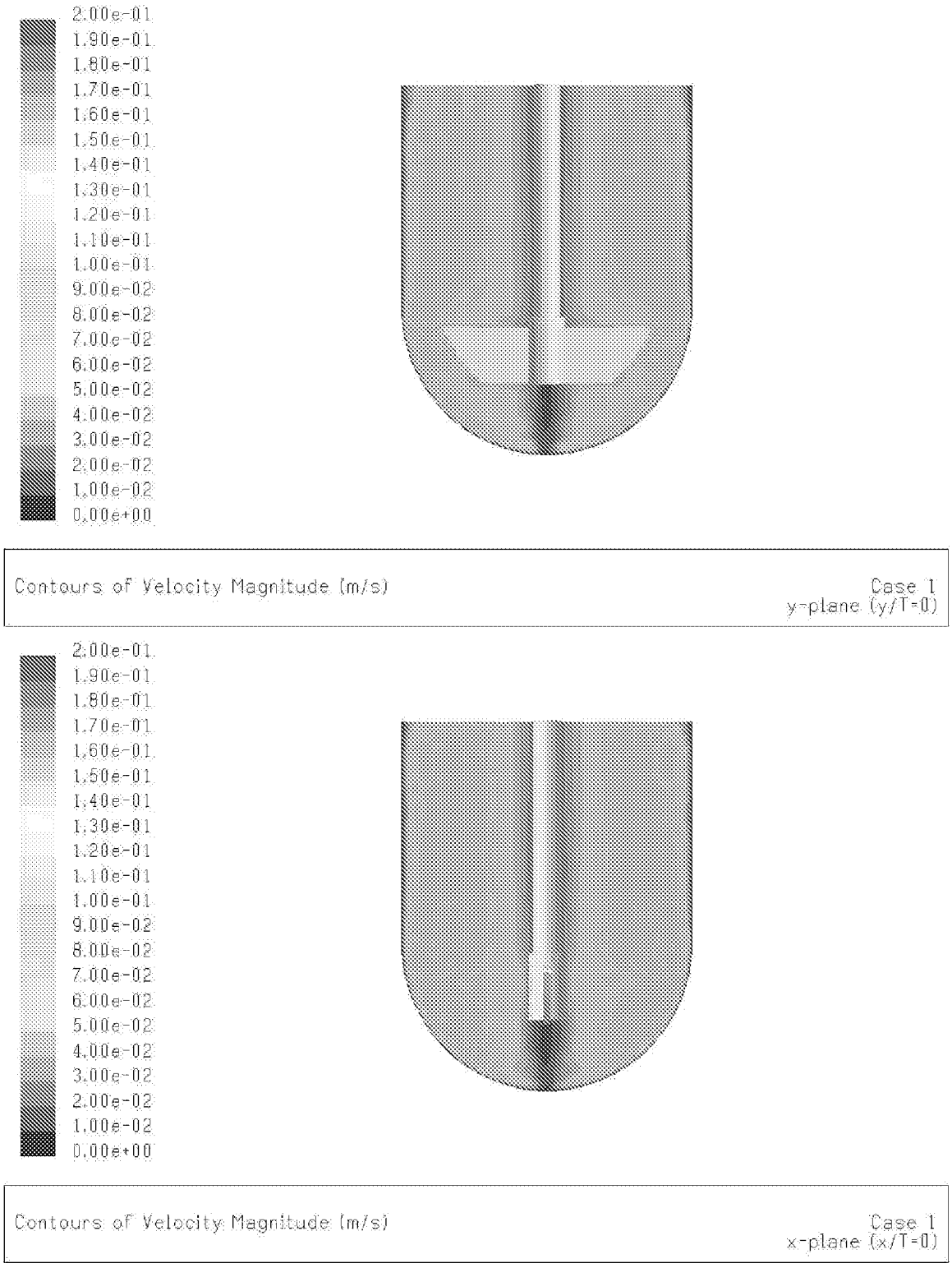



Figure 3. CFD predictions of velocity magnitude contour plots on vertical cross sections through the paddle shaft at different paddle orientations (m/s)

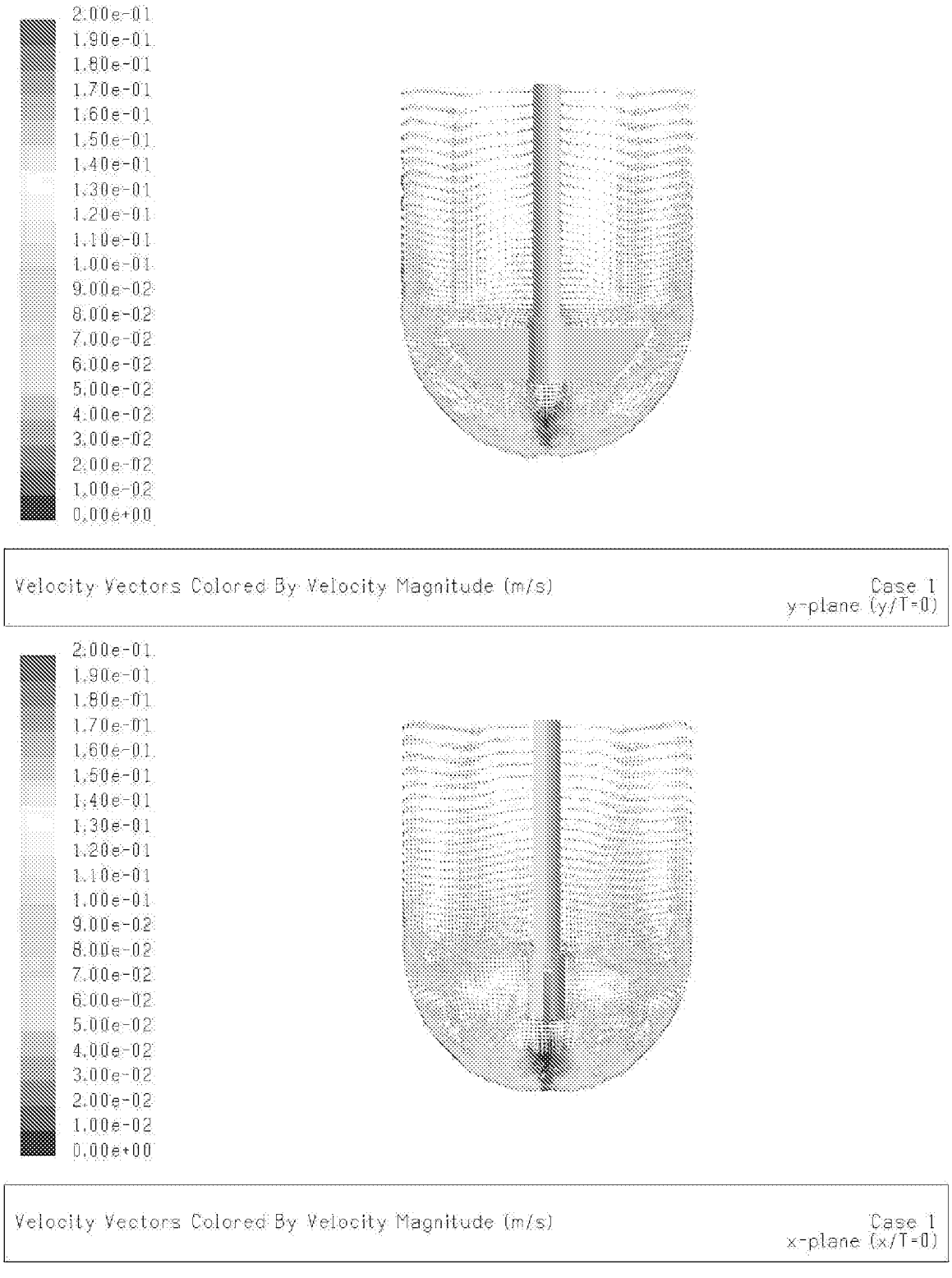



Figure 4. Velocity vectors on a vertical cross section of the vessel at different paddle orientations.

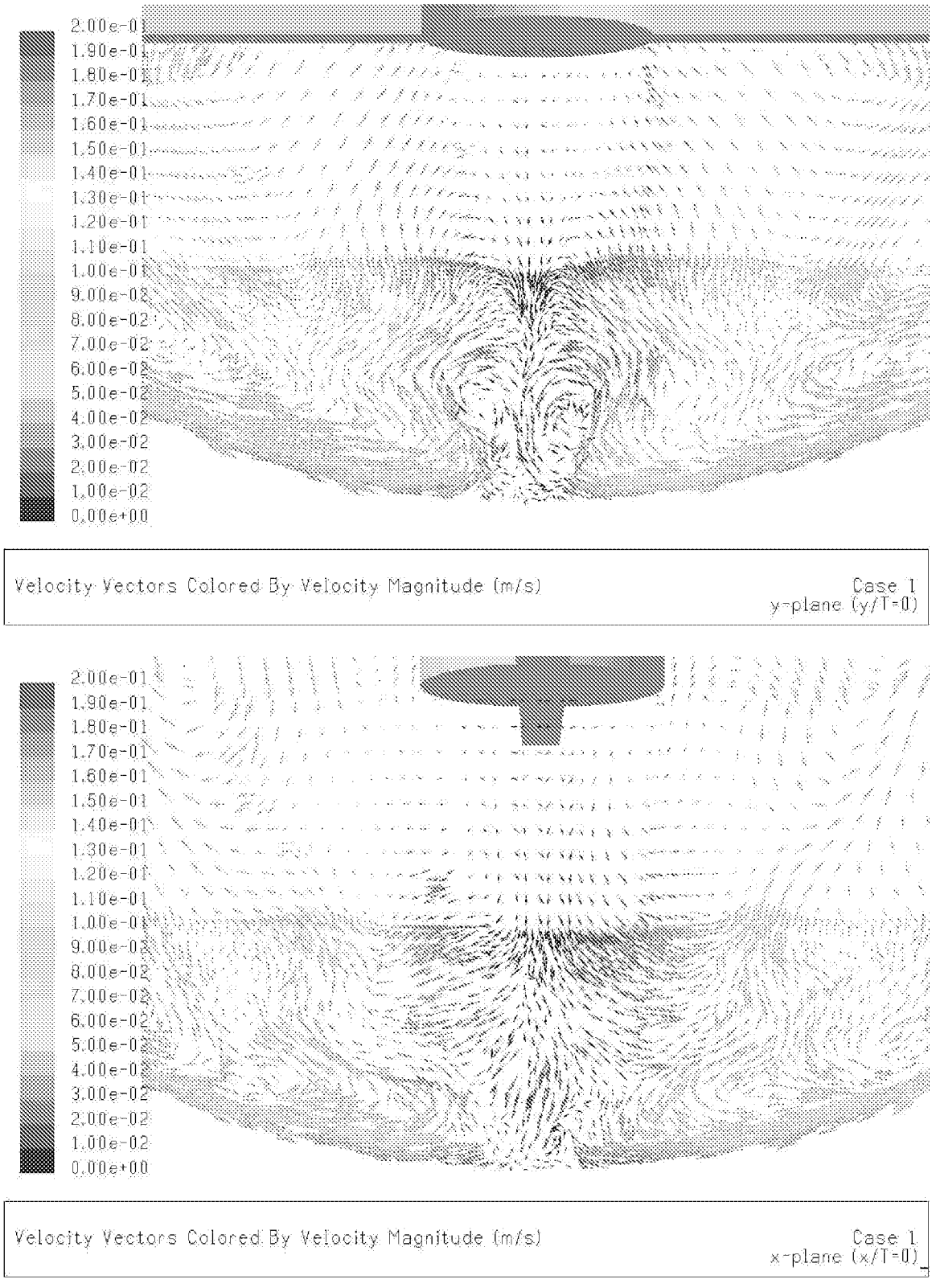
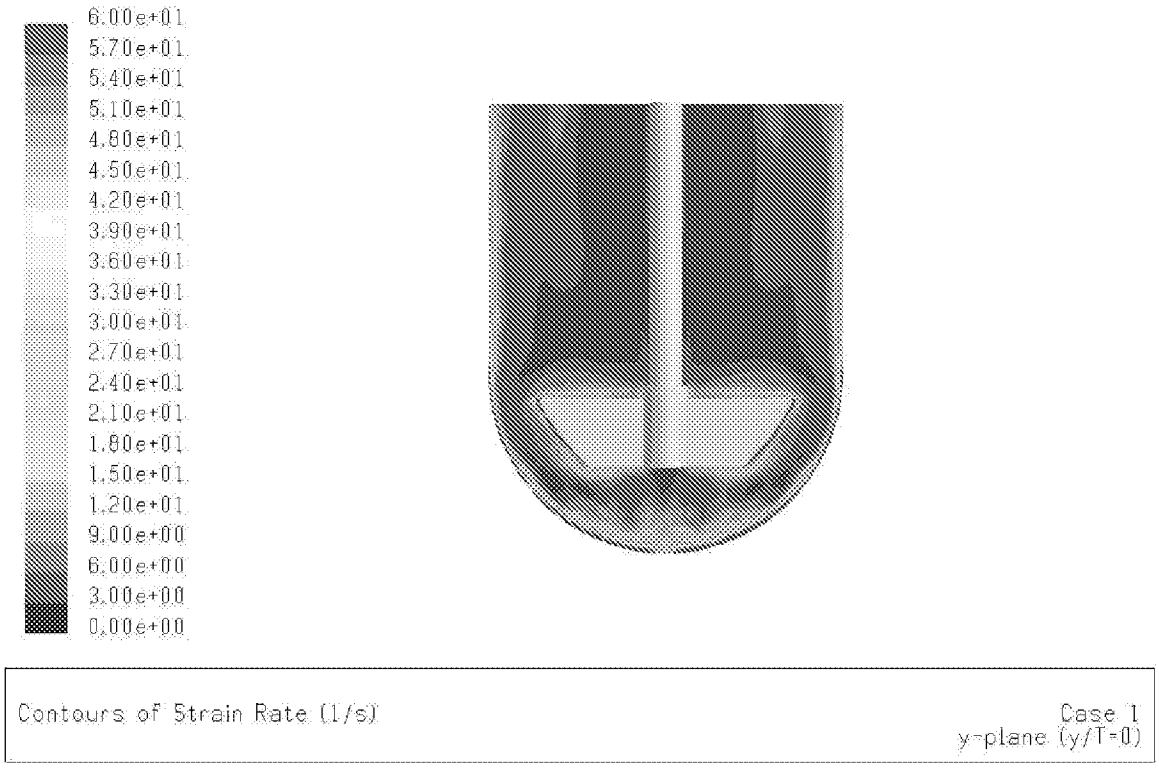



Figure 5. Velocity vectors on a vertical cross section of the vessel at different paddle orientations (bottom of vessel).



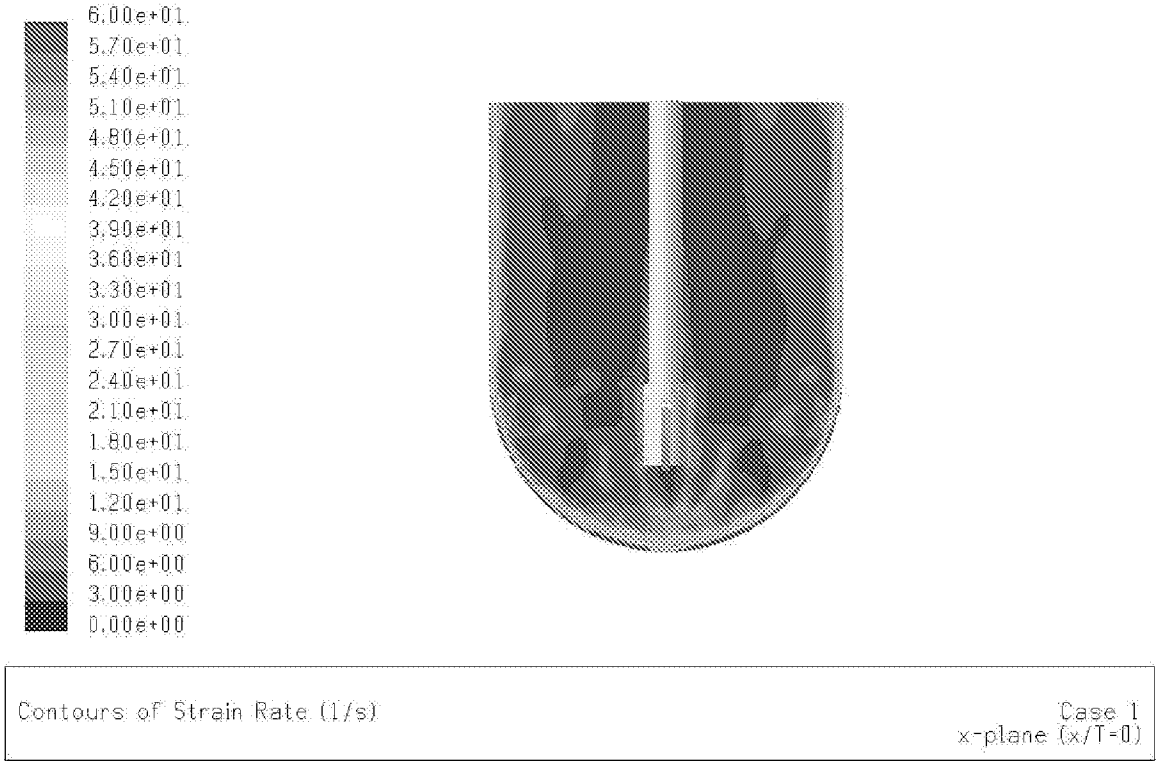




Figure 6. Contours of strain rate on a vertical cross section of the vessel. The red color indicates values of the variable greater than, or equal to, the upper limit shown on the vertical scale.

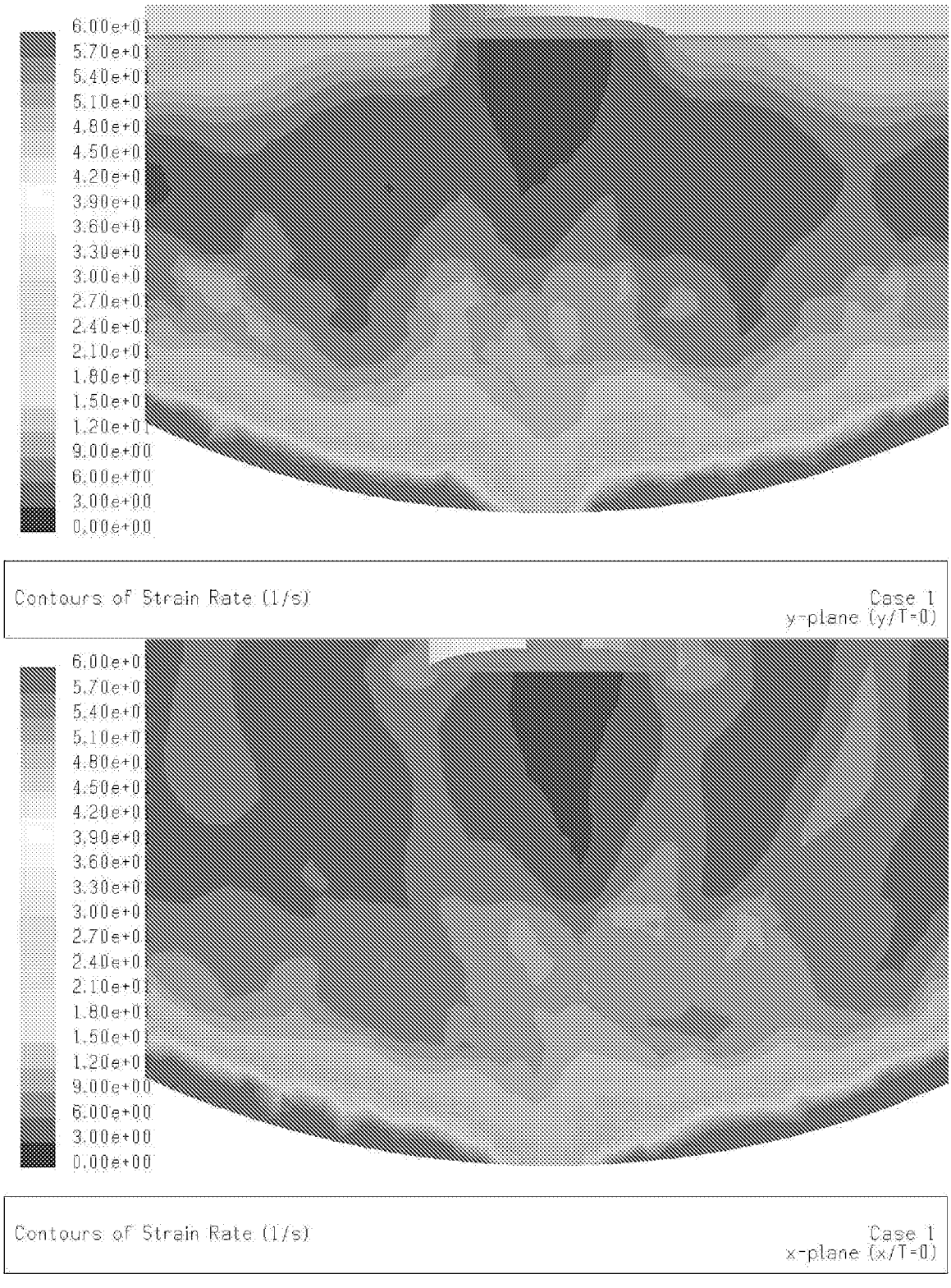



Figure 7. Contours of strain rate on a vertical cross section of the vessel (bottom of vessel). The red color indicates values of the variable greater than, or equal to, the upper limit shown on the vertical scale.

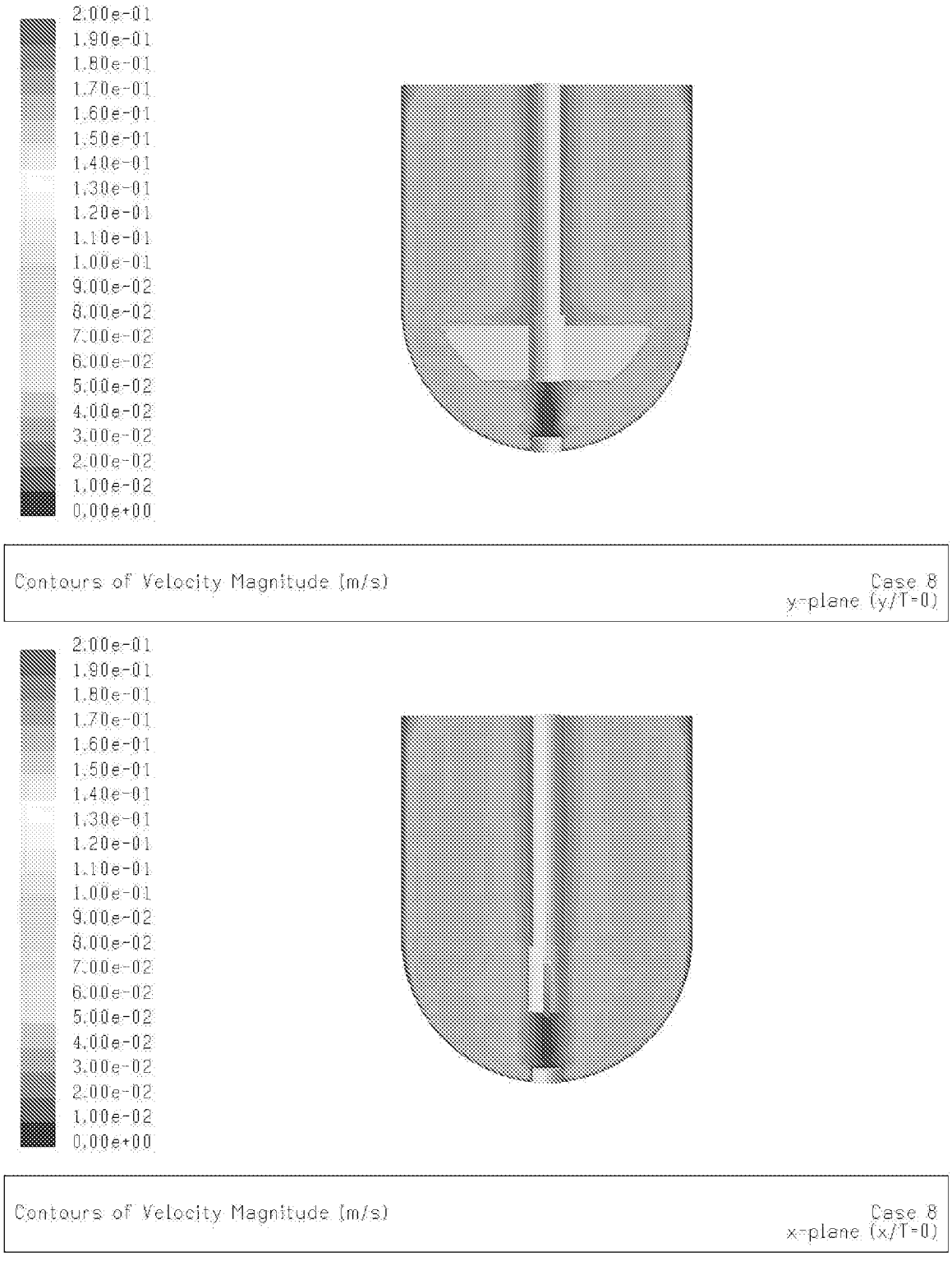



Figure 8. CFD predictions of velocity magnitude contour plots on vertical cross sections through the paddle shaft at different paddle orientations (m/s) assuming the presence of a particle on the vessel bottom.

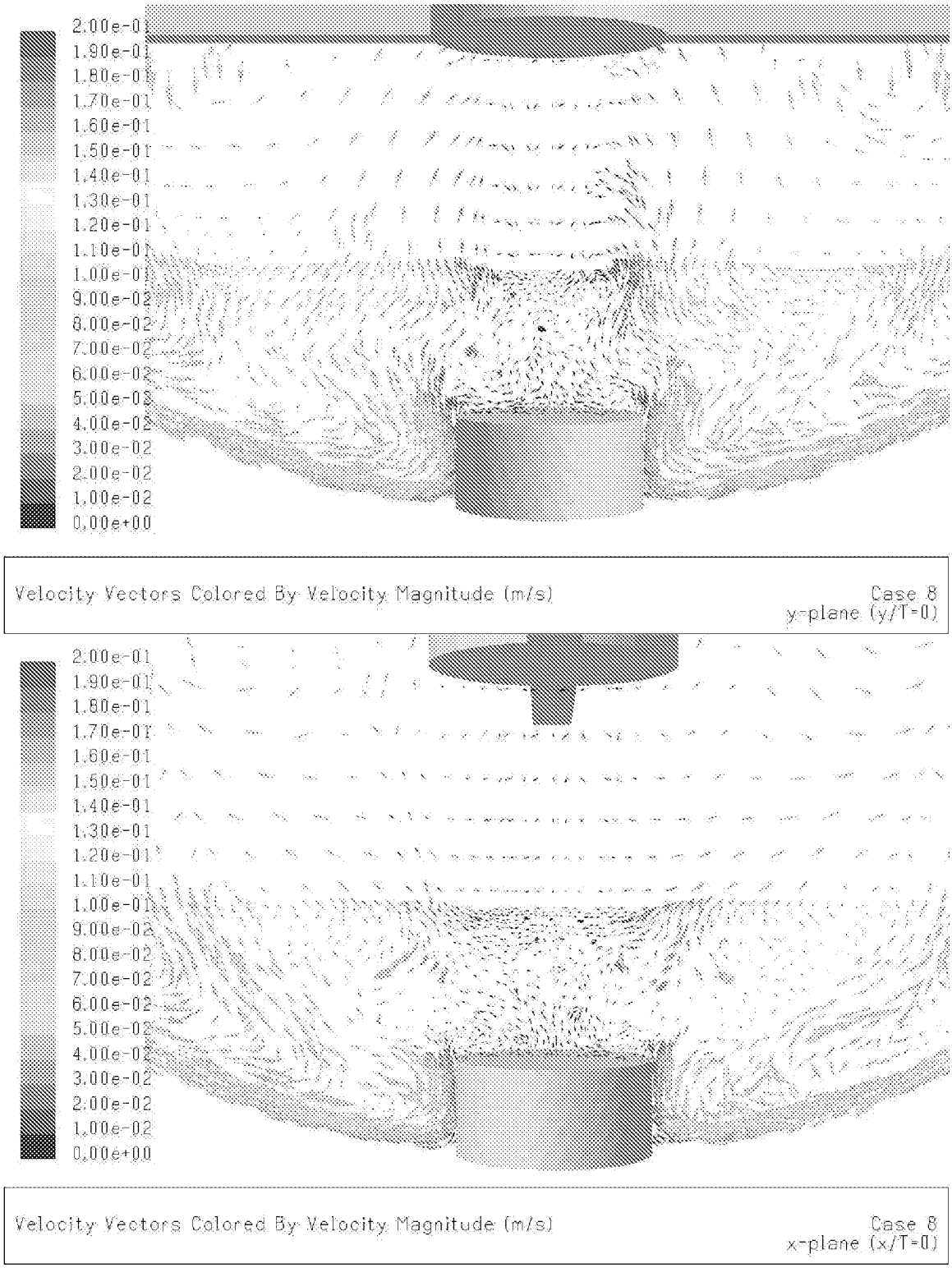



Figure 9. CFD predictions of velocity magnitude contour plots on vertical cross sections through the paddle shaft at different paddle orientations (m/s) (bottom of vessel) assuming the presence of a particle on the vessel bottom.

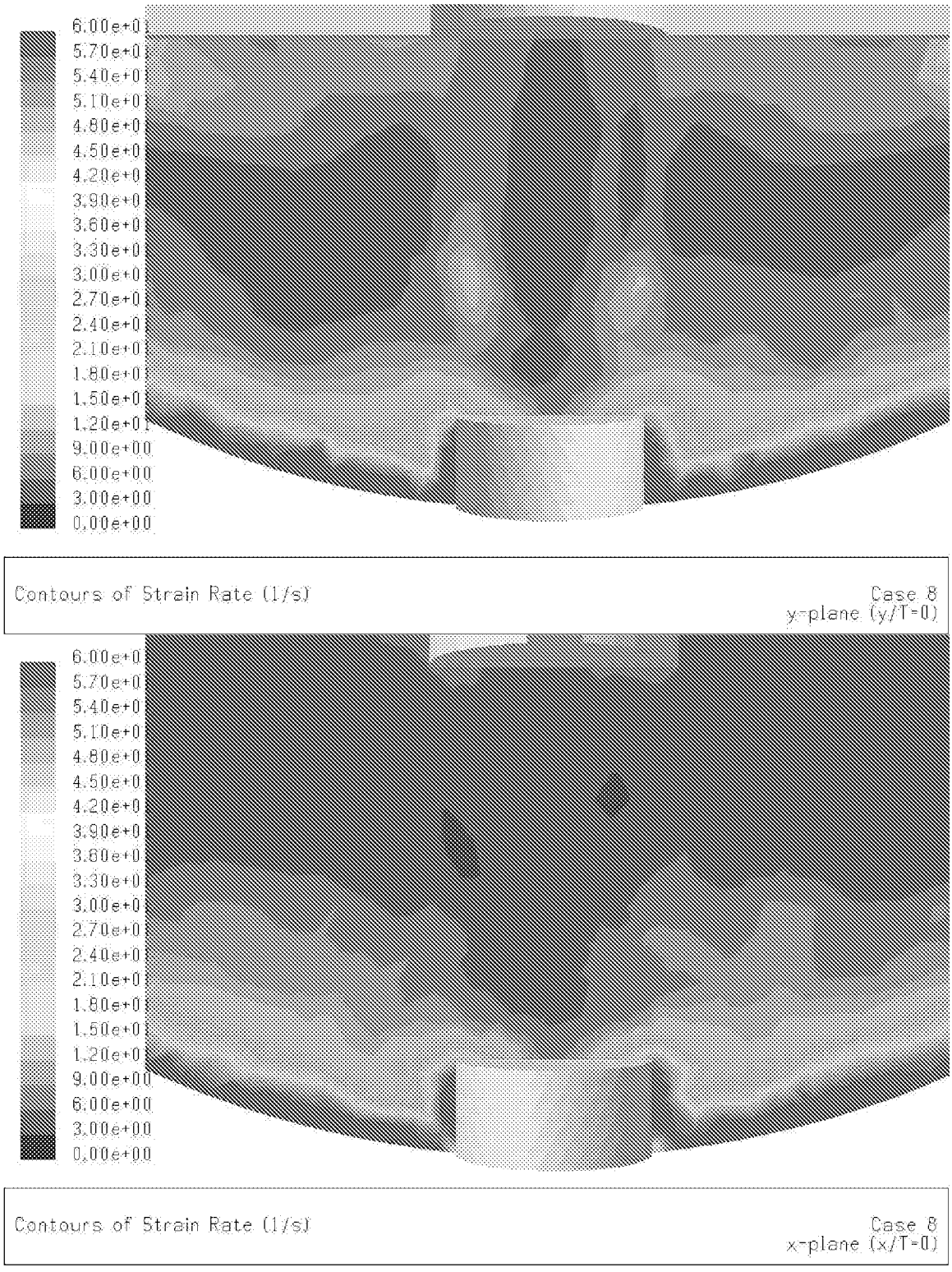



Figure 10. Contours of strain rate on a vertical cross section of the vessel (bottom of vessel). The red color indicates values of the variable greater than, or equal to, the upper limit shown on the vertical scale.

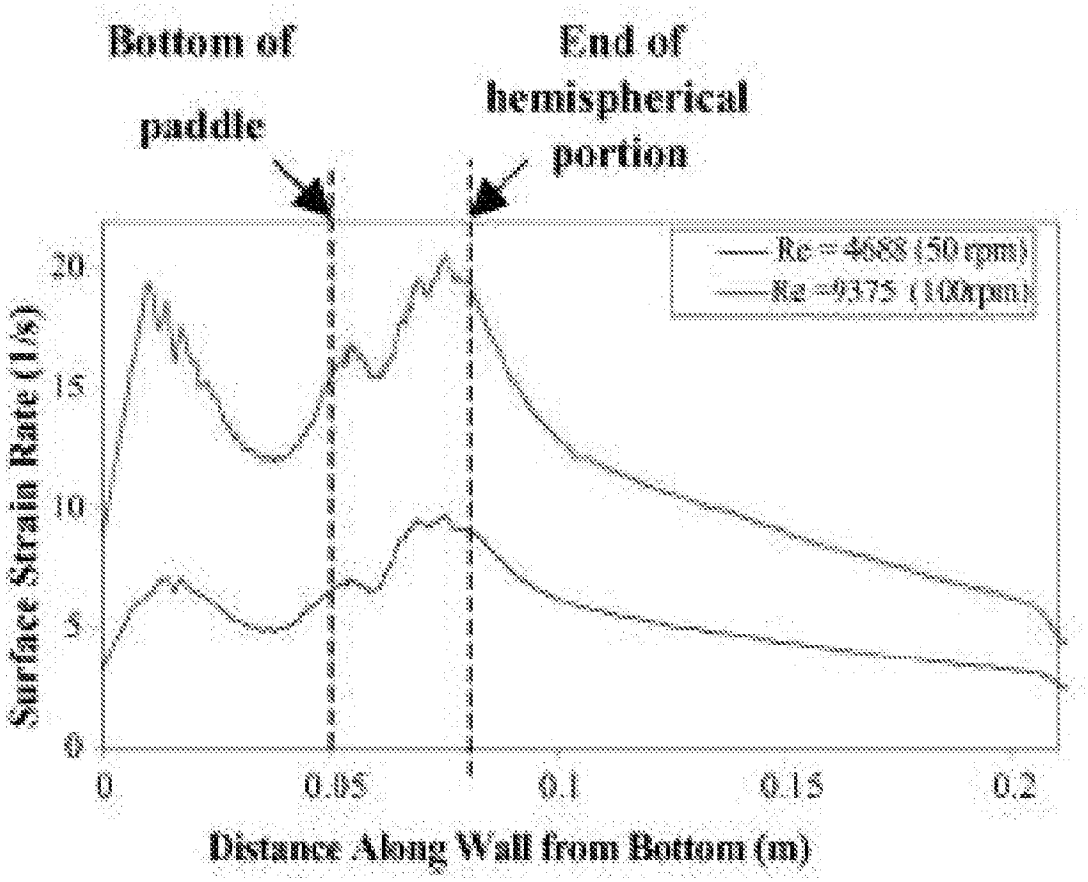



Figure 11. Average rate of strain along the wall as a function of distance.

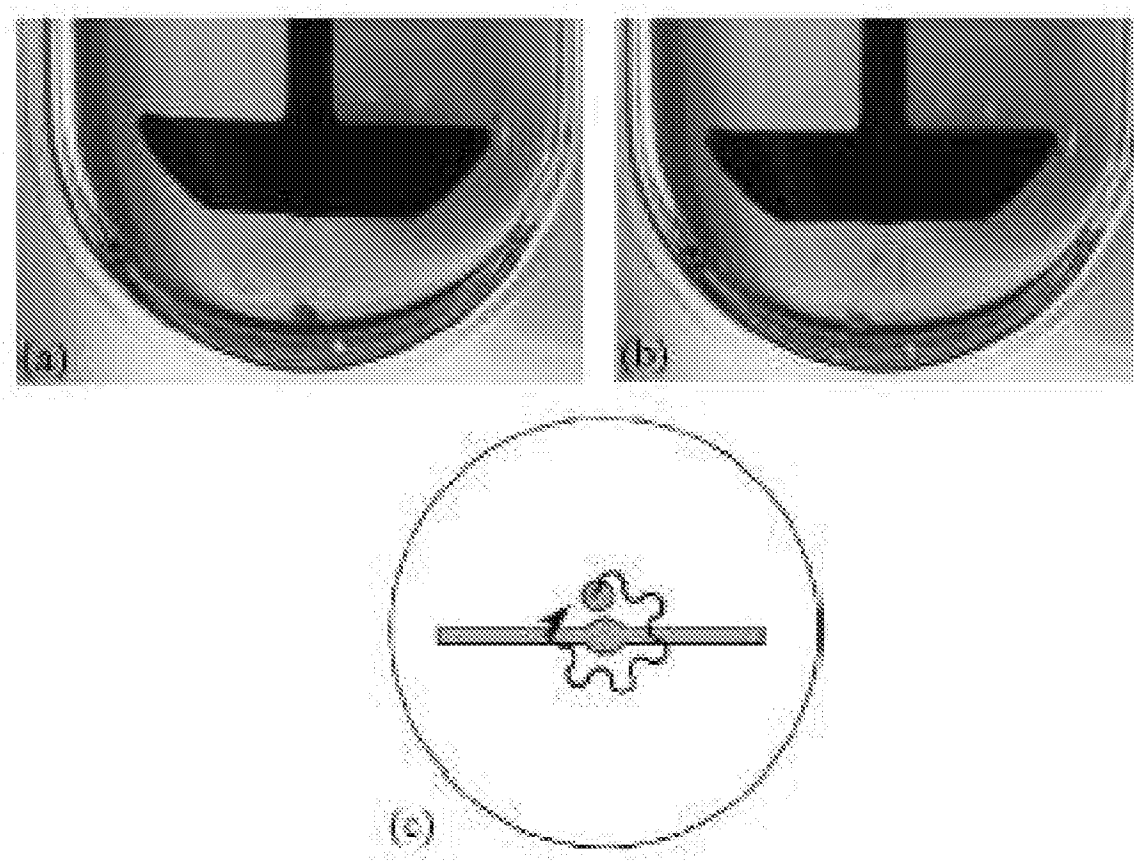



Figure 12. Visualization of tablet movement in the USP dissolution test under typical operating conditions. (a and b) Photographs of tablets movement during visualization experiments, and (c) illustration of tablet movement during the experiment.

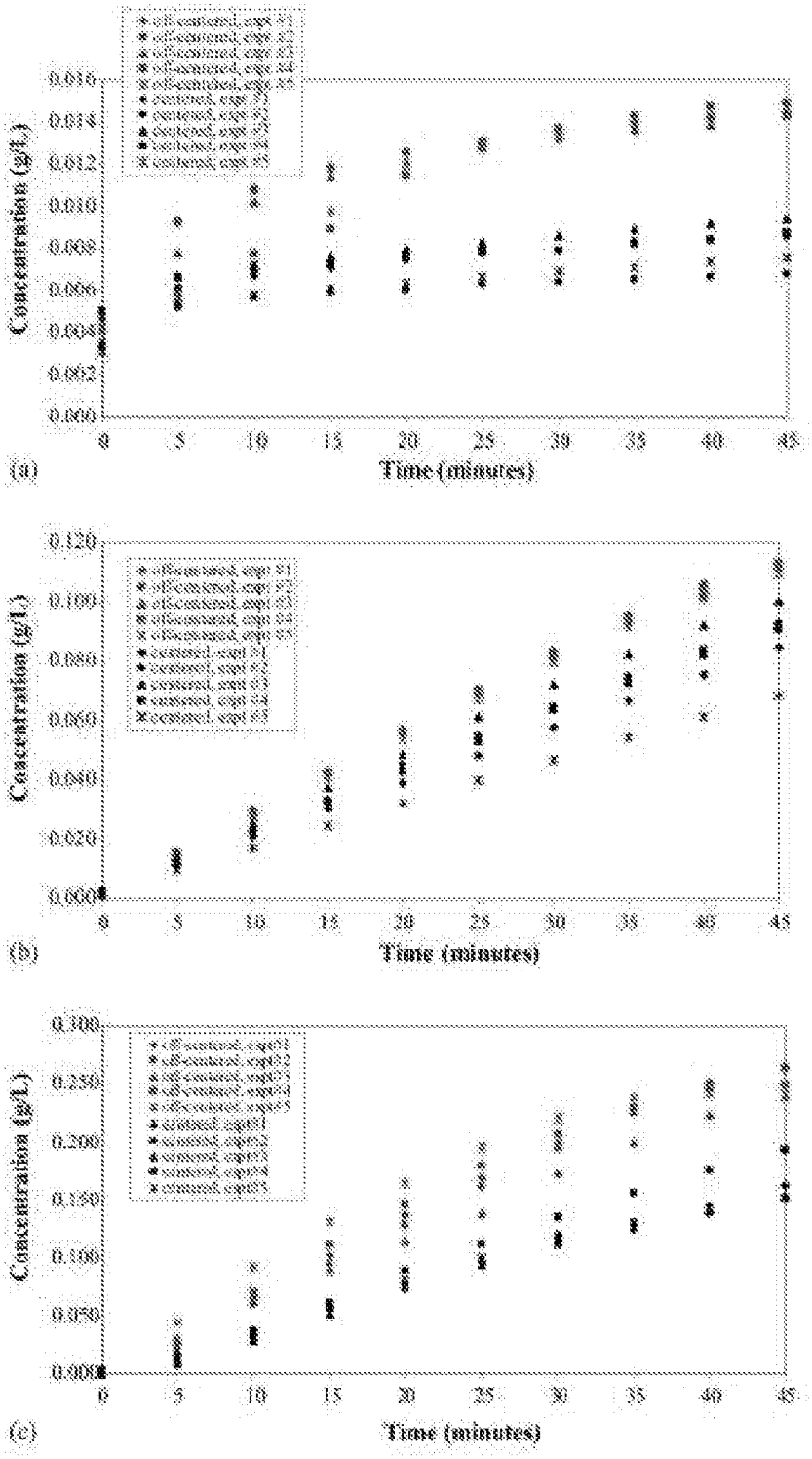



Figure 13. Measured dissolution rate changes resulting from changes in tablet position for (a) prednisone calibrator tablets, (b) salicylic acid calibrator tablets, and (c) naproxen sodium tablets.